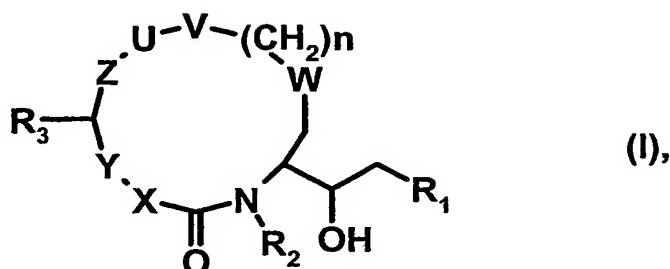


Claims

1. A compound of the formula



in which

R_1 is $\text{CH}(R_a)\text{C}(=\text{O})\text{N}(R_a)R_b$ or $(\text{CH}_2)_k\text{N}(R_c)R_d$, wherein

k is 0, 1 or 2;

R_a and R_b , independently, are hydrogen or an optionally substituted (C_{1-8}) alkyl,

(C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl (C_{1-4}) alkyl, aryl, aryl (C_{1-4}) alkyl, heteroaryl or heteroaryl (C_{1-4}) alkyl group,

R_c and R_d , independently, are hydrogen or an optionally substituted (C_{1-8}) alkyl,

(C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl (C_{1-4}) alkyl, aryl, aryl (C_{1-4}) alkyl, heteroaryl, heteroaryl (C_{1-4}) alkyl, chroman-4-yl, isochroman-4-yl, thiochroman-4-yl, isothiochroman-4-yl, 1,1-dioxo-1 λ^6 -thiochroman-4-yl, 2,2-dioxo-2 λ^6 -isothiochroman-4-yl, 1,2,3,4-tetrahydro-quinolin-4-yl, 1,2,3,4-tetrahydro-isoquinolin-4-yl, 1,2,3,4-tetrahydro-naphthalen-1-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1 λ^6 -benzo[e][1,2]thiazin-4-yl, 2,2-dioxo-1,2,3,4-tetrahydro-2 λ^6 -benzo[c][1,2]thiazin-4-yl, 1,1-dioxo-3,4-dihydro-1H-1 λ^6 -benzo[c][1,2]oxathiin-4-yl, 2,2-dioxo-3,4-dihydro-2H-2 λ^6 -benzo[e][1,2]oxathiin-4-yl, 2,3,4,5-tetrahydro-benzo[b]oxepin-5-yl or 1,3,4,5-tetrahydro-benzo[c]oxepin-5-yl group, or

R_a and R_b , or R_c and R_d , together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or piperazinyl group; and

R_e is optionally substituted (C_{1-8}) alkyl, (C_{1-4}) alkoxy (C_{1-4}) alkyl, (C_{3-7}) cycloalkyl or (C_{3-7}) cycloalkyl (C_{1-4}) alkyl;

R_2 is hydrogen or (C_{1-4}) alkyl;

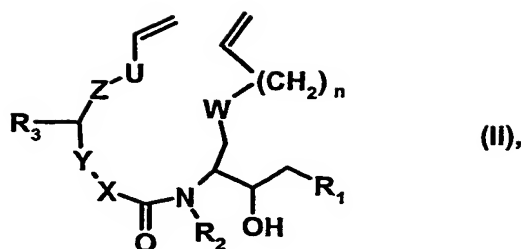
R_3 is hydrogen, (C_{1-6}) alkyl or an optionally substituted (C_{1-6}) alkylOC(=O)NH, (C_{3-7}) cycloalkylOC(=O)NH, (C_{3-7}) cycloalkyl (C_{1-4}) alkylOC(=O)NH, aryl (C_{1-4}) alkylOC(=O)NH, heteroaryl (C_{1-4}) alkylOC(=O)NH, (C_{1-4}) alkylC(=O)NH, (C_{3-7}) cycloalkylC(=O)NH,

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arylC(=O)NH, aryl(C₁₋₄)alkylC(=O)NH, heteroarylC(=O)NH or heteroaryl(C₁₋₄)alkylC(=O)NH group;

- U is a bond, CF₂, CF₂CF₂, CHF, CHFCHF, cycloprop-1,2-ylene, (C₁₋₃)alkylenoxy, (C₁₋₈)alkylene, NR_g or an aromatic or heteroaromatic ring, which ring is optionally substituted with halogen, (C₁₋₄)alkoxy, hydroxy or (C₁₋₄)alkyl, whereby Z and V are in ortho- or meta-position to each other, wherein R_g is hydrogen, (C₁₋₈)alkyl or (C₃₋₇)cycloalkyl;
- V is CH=CH, cycloprop-1,2-ylene, CH₂CH(OH), CH(OH)CH₂ or CR_hR_hCR_hR_h, wherein each R_h, independently, is hydrogen, fluorine or (C₁₋₄)alkyl;
- W is (C₁₋₈)alkylene, O, S, S(=O)₂, C(=O), C(=O)O, OC(=O), N(R_f)C(=O), C(=O)NR_f or NR_f, wherein R_f is hydrogen or (C₁₋₄)alkyl;
- X is an optionally substituted (C₁₋₄)alkanylylidene, (C₁₋₄)alkylene, (C₃₋₇)cycloalkylene, piperidin-diyl, pyrrolidin-diyl, benzothiazole-4,6-diyl, benzoxazole-4,6-diyl, 1H-benzotriazole-4,6-diyl, imidazo[1,2-a]pyridine-6,8-diyl, benzo[1,2,5]oxadiazole-4,6-diyl, benzo[1,2,5]thiadiazole-4,6-diyl, 1H-indole-5,7-diyl, 1H-indole-4,6-diyl, 1H-benzimidazole-4,6-diyl or 1H-indazole-1,6-diyl group or an optionally substituted aromatic or heteroaromatic ring, whereby Y and C(=O)NR₂ are in meta-position to each other;
- Y is a bond, O, S(=O)₂, S(=O)₂NR_g, N(R_g)S(=O)₂, NR_g, C(R_g)OH, C(=O)NR_g, N(R_g)C(=O), C(=O)N(R_g)O or ON(R_g)C(=O), wherein R_g is hydrogen, (C₁₋₈)alkyl or (C₃₋₇)cycloalkyl;
- Z is O, CH₂, CF₂, CHF, cycloprop-1,2-ylene or a bond; and
- n is 0 to 5,
- the number of ring atoms included in the macrocyclic ring being 14, 15, 16 or 17, in free base form or in acid addition salt form.

2. A process for the preparation of a compound as defined in claim 1 of the formula I, in free base form or in acid addition salt form, comprising the steps of cyclisation by metathesis of a compound of the formula



(II),

in which R₁, R₂, R₃, U, W, X, Y, Z and n are as defined for the formula I, in the presence of a catalyst, for instance a ruthenium, tungsten or molybdenum complex, optionally followed by reduction, oxidation or functionalisation of the resulting carbon-carbon-double bond, and of recovering the so obtainable compound of the formula I in free base form or in acid addition salt form.

3. A compound according to claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound according to claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use in the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

5. A pharmaceutical composition comprising a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as active ingredient and a pharmaceutical carrier or diluent.

6. The use of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

7. The use of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

8. A method for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation in a subject in need of such treatment, which comprises

administering to such subject a therapeutically effective amount of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, and a second drug substance, for simultaneous or sequential administration.